COMMENTARY

Cancer Cachexia: Pathophysiologic Aspects and Treatment Options

Erkan Topkan[1]*, Ali Aydin Yavuz[2], Ozgur Ozyilkan[3]

Abstract

Cancer cachexia is a syndrome characterized with progressive weight loss and abnormal wasting of fat and muscle tissue, and affects 40 to 85% of all terminally ill patients, accounting more than 20% of all cancer deaths. Current treatment for cancer cachexia principally depends on its prevention rather than reversing the present disease state, and the clinical results are far from being satisfactory. Although the exact mechanism and predisposing factors have yet to be clarified in detail, our growing knowledge about the pathophysiology and biochemical changes considering this life threatening condition should help in development of future therapeutic strategies. In the present paper, the current preclinical and clinical features considering the pathophysiology and treatment of cancer related cachexia are reviewed.

Key Words: Anorexia - cachexia - cancer - pathophysiology - treatment

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Introduction

Cachexia, "bad condition" in Greek, is a paraneoplastic syndrome in which skeletal muscle mass and adipose tissue are progressively wasted. Incidence of cancer cachexia (CC) in patients with a cancer diagnosis varies with the tumor type but it affects more than 50% of the total (Tishdale, 2004). CC is diagnosed in nearly 40% of patients with sarcoma and breast carcinoma, but it affects as many as 85% of patients with stomach and pancreatic carcinomas (De Wys et al., 1980). Severity of weight loss has been shown to have a negative impact on patients' performance, quality of life (QoL), probability of responding to palliative chemotherapy and treatment for fatigue and pain in advanced pancreatic carcinoma (Persson and Glimelius, 2002). Patients with head and neck cancer experiencing weight loss greater than 20% of their total body weight were shown to be at an increased risk of toxicity and mortality (Ravasco et al., 2005). Longer survival was reported in patients without clinical findings of CC compared with cachectic counterparts (De Wys et al., 1980). As a cause itself the CC accounts more than 20% deaths in terminally ill patients (Inui, 2002).

Severe and progressive loss of fat-free mass which involves only skeletal muscle and not visceral protein reserves and reflects decreases in both cellular mass and intracellular potassium concentration, indicating a bioenergetic deficit. Cachexia related muscular changes reduce muscle strength and increase fatigue during contraction which may result with erosive changes in respiratory muscles and hypostatic pneumonia and finally death due to respiratory insufficiency (Tishdale, 2003). Thus, in the past, CC was frequently considered to be a very late and unfortunately irreversible condition in natural history of cancer and its management was considered as an integral part of palliative and supportive care in terminal stage cancers. However, contradictory with this traditional belief, the presence of some degree of weight loss in 60% of some gastrointestinal tumors and 80% of lung cancers upon diagnosis suggest that CC should be considered as an "early event" at onset of disease (Inui, 2002).

In support to this suggestion, more recent findings considering the metabolic, biochemical, and molecular changes showed that most of the factors which are currently believed to be involved in occurrence and progression of CC were present at the time of diagnosis even in the absence of weight loss (Rossi Fanelli et al., 1995). Chemotherapy (CT) and radiation therapy (RT) have proven efficacy in many cancer types, when used alone or concurrently as the sole treatment choice or adjunct to surgery. However patients receiving CT and/or RT are at further risk of nutritional risk and resultant cachexia progression due to possible side effects such as anorexia, mucositis, taste changes, dysphagia, odynophagia, xerostomia, dysgeusia, nausea, vomiting, and diarrhea (Dietel and To, 1987). The scenario is worse in patients receiving concurrent chemoradiotherapy such

*[1]Department of Radiation Oncology [2]Department of Radiation Oncology, Baskent University, [3]Department of Medical Oncology, Baskent University, Adana Treatment and Research Centre, Adana, Turkey *For Correspondence: Department of Radiation Oncology, Baskent University Medical Faculty, Adana Research and Treatment Centre, 01120, Adana/ TURKEY Fax: +90 322 3227979 E-mail: drerkantopkan@yahoo.com*

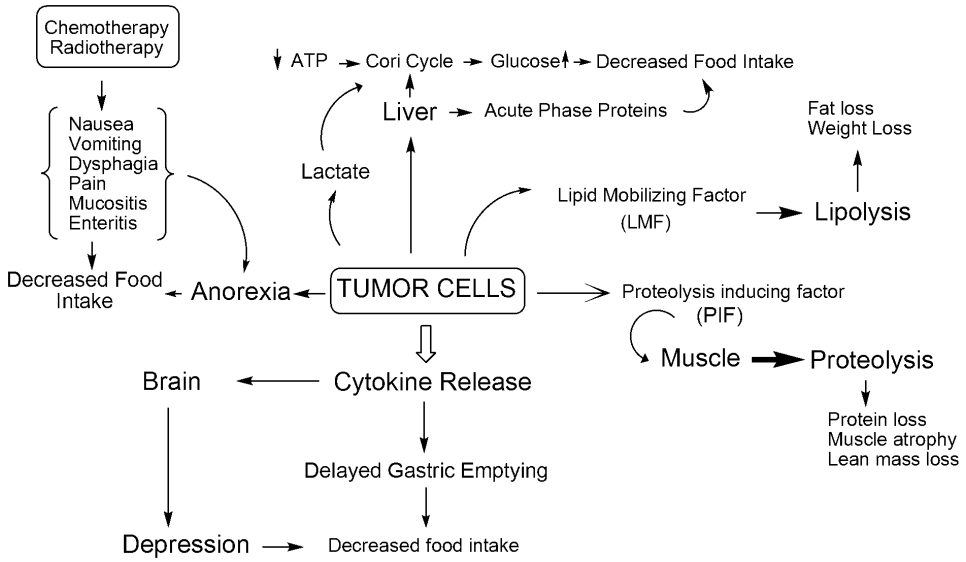

Figure 1. Multiple Central and Peripheral Factors Play Roles in Pathogenesis of Cancer Cachexia

as head and neck cancers because of further sensitizing effects of CT on RT. Changes related with malnutrition and anorexia may increase risk of infections, treatment toxicity, decreased response to treatment, decreased disease free and overall survival, QoL, and treatment costs (Grant and Rivera, 1994). Although great effort has been spent yet the main approach for CC treatment is aimed at its prevention rather than reversing the metabolic pertur bations, thus understanding of exact pathophysiological consequences of CC is needed for the development of new treatment modalities.

Pathophysiology of Cancer Cachexia

The exact pathopysiologic mechanisms of CC is unclear but is believed to be multifactorial including tumor and host derived factors. Hypotheses about the mechanisms of cancer related anorexia and cachexia have evolved from animal tumor models and unfortunately there is little corroboration of the proposed pathophysiology in human studies. Our understanding of normal appetite signals may provide evidence for future clinical research in experimental animal models and human studies.

Normal Appetite: Normal appetite involves peripheric and central pathways. Peripheric appetite control has four phases of normal hunger and satiety cycles. Gastric motility phase governs gastric motility by vagal signals from the nucleus tractus solitarious to the sub adjacent dorsal motor nucleus. Postabsorbtive phase is mediated by cholecystokinin release from duodenum, which functions by binding to vagal cholecystokinin-A receptors and reduce motility via nucleus tractus solitarius. The metabolic phase is controlled by down modulation of neuropeptide-Y (NPY) neurons in the arcuate nucleus of the hypothalamus by combined interaction of hepatic glucose and insulin, and adipocyte release of leptin, latter being a powerful anorexigenic factor. And finally, an ileal phase which includes the inhibition of gastric motility by glucagon-like peptide-1 induced inhibition of hypothalamic strong orexigen NPY release (Davis et al., 2004).

Central appetite control depends on the balance between energy inputs and resting energy expenditure governed by a parallel system of NPY and pro-opiomelanocortin (POMC) neurons arising from hypothalamic arcuate nucleus. Although thyroid releasing hormone, corticotrophin releasing hormone, oxytocin, orexin, and melanocortin-concentrating hormone serve as secondary effectors, the NPY and POMC are regulated primarily by leptin and serotonin. NPY and agouti-gene related transcript (AGRP) is the main appetite stimulating central neurotransmitters with separate but synergistic appetite response. POMC reduces appetite by opposing the actions of NPY. Leptin is the dominant negative peripheral NPY regulator secreted by white adipocytes. Serotonin inhibits NPY neuron activity through postsynaptic 5HT1b and 5HT1c receptors and cause satiety. Furthermore, coordination of normal appetite signals and basal metabolic rate is regulated by NPY and POMC activity. NPY increases parasympathetic activity and decrease resting energy expenditure whereas POMC activity counteracts with NPY and increases resting energy expenditure by activating sympathetic output (Davis et al., 2004).

Pathologic factors in pathogenesis of CC include anorexia and related decreased food intake, alterations in energy and substrate metabolism, and accelerated fat and muscle loss. The cancer related anorexia has a complex and multifactorial pathogenesis which implies impaired coordination of the central and peripheral pathways regulating normal eating behavior. Decreased desire for eating which may be caused by cancer itself or anti-neoplastic therapy related factors including mechanical obstruction in the gastrointestinal tract, mucositis, infections, nausea, vomiting, dysphagia, malabsorption, pain, and depression are contributing factors that accelerate the cachectic process (Barber et al., 1999). The pathopysiologic mechanisms of CC are briefly summarized in Figure 1.

Alterations in energy and substrate metabolism have long been known to play important roles in pathogenesis of CC. Besides significant reduction in food intake, increased resting energy expenditure due to the impaired balance between pro- and anti-inflammatory cytokines appears to be an essential factor for CC progression (Argiles and Lopez-Soriano, 1998). Tumor necrosis factor-α (TNF-α), Interleukin (IL)-1, IL-2, IL-6, Interferon-γ are the pro-inflammatory factors excessive elaboration of which has been implicated as probably the most common cause of various types of cachexia including CC (Argiles and Lopez-Soriano, 1998). Whereas, IL-4, IL-12, IL-15 are the anti-inflammatory factors defending the body against the affects of cachectic factors. The activation of pro-inflammatory cytokines cause activation of nuclear transcription factor-κB (NF- κB) that leads to inhibition of muscle protein synthesis (Wheeler et al., 1999), and reduction of Myo D protein which is a transcription factor that principally modulates signaling pathways involved in muscle development (Acharyya et al., 2004). Myo D binding to myosin heavy chain IIb is essential for myosin expression in fast twitch muscles, but inhibition of the mRNA synthesis for myosin heavy chain by synergistic actions of TNF-α and Interferon-γ deters muscle development and cause proteolysis of myosin heavy chain (Wheeler et al., 1999; Acharyya et al., 2004). Furthermore, pro-inflammatory cytokines activate ubiquitin–mediated proteolysis, which is accepted as the major system involved in disease-induced catabolic states (Mitch and Goldberg, 1996). Ubiquitin also indirectly inhibits protein synthesis and accelerates proteolysis by inhibition of inhibitory KB-protein (IKB) which is the strong inhibitor of NF- KB. Proteolytic activity of ubiquitin is propagated further by activation of cortisol, and catecholamine release leads a state of increased resting energy expenditure (Pende et al., 1990).

Cytokines also delay gastric emptying, lower serum albumin concentrations, and cause severe fat loss by enhancing lipolysis (Davis et al., 2004). Fat loss is a prominent characteristic of CC and may be severe enough to reach 85% of total fat mass in case of total body weight loss reaching 30% (Fearon, 1992). Although the cytokines are strong lipolytic factors, increased lipid mobilization in CC is attributed to an α-2 glycoprotein tumor catabolic factor called lipid mobilizing factor (LMF). Similar with lipolytic hormones, LMF directly acts on adipocytes and cause release of free fatty acids and glycerol in to circulation (Beck and Tishdale, 1987). Furthermore LMF increases the sensitivity to lipolytic stimuli through a variation in G–protein expression and stimulates triglyceride hydrolysis in adipocytes by stimulation of adenylate cyclase in a GTP-dependent process (Hirai et al.,1998). The severe progressive loss of muscle mass is the most evident and threatening feature of CC. Normally, there is a balance between the rates of muscle protein breakdown and synthesis but this balance has been shown to be impaired in favor of muscle breakdown with resultant muscle atrophy (Langhans, 2002). Two proteolytic pathways have been suggested to cause muscle hyper catabolism, those are the hyperactivation of calcium-dependent and ATP-ubiquitin-dependent pathways (Langhans, 2002). In animal models activation of calpains (calcium-dependent proteases) has been shown to be necessary for the initial myofibrillary protein degradation with resultant release of actin and myosin. This myolytic process renders actin and myosin available for further degradative processes (Williams et al., 1999). Recent evidence from an animal model confirmed the role of calpains in increased protein degradation in CC related muscle loss (Costelli et al, 2002). Cytokine blockade was reported to effectively reduce calpain activity and prevent muscle loss in tumor inoculated rats. Proteolysis inducing factor (PIF), a host derived factor, which was first isolated by Todorov et al (1996) in the urine of weight-losing cancer patients including breast, ovarian, colorectal and pancreatic cancers irrespective of tumor type exerts a strong catabolic action on muscle mass and cause severe loss in total and lean body mass (Cariuk et al., 1997).

The ATP-ubiquitin dependent pathway plays an essential role in CC related muscle changes. This system has complex structural and functional units and up regulation of this system has been reported in wasting conditions such as trauma, burns, sepsis, acidosis, renal failure, and various cancers (Costelli et al., 1993; Tiao et al., 1997). In a recent study it has been shown that ubiquitin mRNA expression was significantly increased in muscle biopsies obtained preoperatively in 20 patients undergoing surgery for gastric cancer (Grant and Rivera, 1994). In another study proteosome proteolytic activity was shown to be significantly increased in gastric cancer patients (Bossola et al., 2001). Findings considering the over expression of ubiquitin mRNA and proteosome proteolytic activities in patients with no significant or even no weight loss, supports the suggestion that the causative factors of CC are operating early during the natural course of cancer, and underscores the need and importance of early intervention.

Treatment Options for Cancer Cachexia

Cancer as a disease and malnutrition are closely linked and can rapidly develop in to a vicious circle, in which disease causes decreased desire for eating, malabsorption and increased loss of nutrients, which in turn cause increased susceptibility to complications, discussed before. These complications further impair the well-being of patient, including fatigue, decreased mobility, poor response to treatment and further complications, which results with further decrease nutritional status. Therefore, CC must be accepted as a self-perpetuating condition. At that point, Ravasco et al (2005) suggested that the breakage of this circle can improve treatment outcomes and quality of life measures, which can be achieved through providing the appropriate medications and nutritional support.

Nutritional Support:

Current therapeutic interventions in CC are of limited benefit, and although despite the fact that nutritional intake is frequently reduced, the treatment with hyper caloric feeding has not been shown to promote weight gain. However, it is important to note that nutritional support has generally been administered in terminal stages of disease when there is little or even no chance to reverse

the condition with any known treatment maneuvers. This reflects the inappropriate use of nutritional supplements in cancer patients. Thus, the aim of nutritional support has to be the halting of nutritional decline and delay or prevent the development of malnutrition. Early nutritional intervention is essential to improve prognosis and outcome by preventing the onset of malnutrition and the vicious circle discussed above.

Nutritional counseling is an important integral part of cancer treatment, and patients requiring nutritional support must be determined at the beginning of anticancer treatment. Several approaches and products can be used, including fortified normal foods, sip feeds and enteral tube or parenteral feeding. Oral nutritional supplementation is the easiest, most practical and noninvasive method but it is frequently handicapped with the need for an intact gastrointestinal function. Therefore, enteral tube or total parenteral nutrition may be considered in some patients. CC is a multifactorial condition thus increasing food intake may not be sufficient to reverse or prevent nutritional decline. As the inflammatory mediators have been shown to play important roles in cachexia onset and progression it may be beneficial to use nutritional supplements with anti-inflammatory properties. Eicosapentaenoic acid (EPA), the major active component of fish oil is such an agent with down regulatory effects on both pro-inflammatory cytokines and PIF (Barber, 2001). The primary action of EPA is to increase lean body mass through attenuation of the increased activity and expression of the ubiquitin-proteasome pathway, which is suggested to be the principle pathway involved in cachexia induced muscle atrophy. The present clinical data supports this suggestion; in one study, administration of oral EPA enriched nutritional support caused significant increase in lean body mass with no change in either fat mass or percentage total body water (Barber et al., 1999). The increased lean body mass is translated into an increased physical activity level reflecting an improved state of QoL (Moses et al., 2004). Recent data from animal studies suggest that combination of EPA with the leucine metabolite beta-hydroxybetamethylbutyrate (HMB) to aid protein synthesis is more effective than EPA alone in reversing CC (Smith et al., 2005). But, clinical studies are needed to confirm this outstanding result in human cancers.

Another attractive method may be the use of nutritional supplements containing agents proven to effectively prevent treatment related toxicities. Glutamine, melatonin and octreotide are such agents. Glutamine has recently been shown to significantly decrease eosophagitis and related complications in patients undergoing RT for lung cancer (Algara et al., 2007). Melatonin has been shown to decrease severity and incidence of chemotherapy induced enteritis (Jahovic et al., 2004), and octreotide has been shown to effectively prevent the CT induced (Zidan et al., 2001), RT induced (Yavuz et al., 2002), and chemoradiotherapy-induced diarrhea (Topkan et al., 2004) in cancer patients. Although the effectiveness of these agents needs to be tested in prevention or treatment of CC, theoretically their preventive properties on treatment related toxicities suggest an important role for them in management of CC. Because, it can be assumed that any decrease in mucositis, diarrhea and malabsorption will theoretically result in improved nutrition and QoL, and decreased loss of weight.

Appetite Stimulants

Corticosteroids have proven efficacy in treatment of CC. Administration of corticosteroids has been shown to increase appetite in patients with gastrointestinal cancers (Moertel et al., 1974). However corticosteroids should perhaps be best reserved for patients with an especially poor prognosis, because challenging side effects such as myopathy can occur with long-term use. Corticosteroids may be good choices in patients with thrombophlebitis as progestational agents are contraindicated in such setting. Progestational agents have also been proven to improve appetite. Administration of megesterol acetate was shown to stimulate appetite and increase non-fluid body mass (Loprinzi et al., 1990). But in a subsequent study megesterol acetate was reported to cause weight gain consisted primarily of fat, not lean tissue (Loprinzi et al., 1993). Although the megesterol acetate is relatively well tolerated by patients, it carries some side effects, including thrombophlebitis, suppression of the pituitary-adrenal axis, male impotence and menstrual bleeding upon abrupt withdrawal.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by inhibiting cyclo-oxygenase enzyme. In a short study, administration of ibuprofen for 7-days was reported to reduce resting energy expenditure and acute phase response, but the body weight was not measured (Wigmore et al., 1995). In another trial co-administration of ibuprofen and megesterol acetate produced a greater increase in body weight than did megesterol acetate alone (Mc Millan et al., 1995). In one study, indomethacin improved some measures of performance and prolonged survival without any effect on total body weight, in patients with metastatic solid tumors (Lundholm et al., 1994).

Thalidomide is a unique drug with multiple immunomodulatory properties and potent inhibitory affects on TNF-α production by enhancing TNF-α mRNA degradation (Sampaio, 1991). Recently, thalidomide has been shown to inhibit NF-KB activity which plays a key role in CC pathogenesis (Gordon., 2003). Gordon et al. (2005) showed that the administration of thalidomide significantly attenuated both the total body weight and lean body mass loss. Enlightened with these encouraging results same group conducted a further large study involving subjects with cachexia secondary to all upper gastrointestinal tumors, and the results of this study is waited with interest.

Pentoxifylline, a phosphodiesterase-4 inhibitor which acts by inhibiting TNF-α production was suggested to be a promising agent but clinically has been shown to fail to improve appetite or induce weight gain (Goldberg et al.,1995). However, it must be considered that the population entered was a heterogeneous group of patients with cancers arising in a variety of primary sites and in various stages of advanced disease. It is amenable that larger trials in the next future will test its real role in the

treatment of CC.

Metoclopromide is a prokinetic agent which is used for treatment of anorexia in two studies (Bruera et al., 2000; Bruera et al., 1994). Fifty-five patients were included and 80 mg/d administered orally was used for 1 to 2 weeks period. There was significant improvement in nausea but no improvement in appetite or caloric intake.

Hydrazine sulphate has been intensively tested but only in one study it was found to increase or stabilize weight and improve appetite (Chlebowski et al., 1987). In the other studies it demonstrated no efficacy on prevention or treatment of cancer-related anorexia and cachexia (Loprinzi et al., 1994; Loprinzi et al., 1994).

Cyproheptadine has been used in two studies by oral administration (Pawlowski, 1975; Kardinal et al., 1990). A total of 344 patients were tested but, although a significant improvement was reported in the first study (Pawlowski, 1975) the second study reported its effectiveness to be no more than placebo by means of appetite improvement and weight gain (Kardinal et al., 1990). Melatonin was tested in two studies including 186 patients (Lissoni et al., 1993; Lissoni et al., 2003). Although weight loss was shown to be decreased by its use, the food intake and appetite did not improve (Lissoni et al., 1993). Asthenia and weight loss greater than 10% was less with melatonin plus CT compared to CT alone (Lissoni et al., 2003). Melatonin has been shown to decrease severity and incidence of CT induced enteritis (Jahovic et al., 2004), which may additionally decrease weight loss and increase QoL.

Erythropoietin was used in two studies including 417 patients (Lundholm K, 2004; Daneryd et al., 1998). It was shown to improve body fat, maximum energy capacity, and energy balance when combined with a COX-2 inhibitor (Lundholm et al., 2004). In the second study erythropoietin and COX-2 inhibitor combination was shown to be superior in comparison with COX-2 inhibitor considering the weight loss, but food intake and lean body mass were reported to be similar between two groups (Daneryd et al., 1998). Erythropoietin appears to add to CC treatment with its powerful antianemic properties. Theoretically, prevention or treatment of anemia may improve chronic fatigue and thus may improve desire for food intake. But this issue waits to be addressed in human trials.

Ghrelin, a growth hormone secratogogue, has been shown to have stimulatory effects on food intake, adiposity and weight gain (Wren et al., 2000). In a study reported by Wren et al (2001) ghrelin was reported to improve appetite in male and female healthy volunteers in a double-blind, randomized, controlled trial. Also when administered subcutaneously, ghrelin was demonstrated to stimulate energy intake in healthy lean human volunteers (Druce et al., 2006).

Androgenic steroids were administered to a total of 512 patients in two studies (Chlebowski et al., 1986; Loprinzi et al., 1999). Addition of nandrolone decanoate to CT showed a trend toward less weight loss with nandrolone compared with CT alone (Chlebowski et al., 1986). In another study, the supplementation with the anabolic steroid fluxymesterone was inferior by means of weight loss and significantly more toxic compared to dexamethasone (Loprinzi et al., 1999).

The cannabinoid dronabinol was studied in a three-arm trial of dronabinol, megesterol acetate, and a combination of both agents (Theobald et al., 2002). Results showed that megesterol acetate was superior to dronabinol in improving anorexia, and combination therapy did not confer any additional benefit over megesterol acetate. Furthermore QoL was reported to be better with megesterol acetate group, especially considering emotional construct.

Mirtazapine is a 5HT2 receptor blocker type antidepressant drug which increases appetite and weight gain as common side effects, but there is little clinical experience considering its use in cancer cachexia (Theobald et al., 2002). Recently two independent groups reported that inhibition of myostatin activity by use of anti-myostatin antibodies resulted in improved muscle function and reduced muscle degeneration in dystrophic mice (Bogdanovich et al., 2002; Wagner et al., 2002). Furthermore, in the study of Bogdanovich et al.. (2002), blockade of endogenous myostatin by injection of blocking antibodies for 3 months caused an increase in body weight, muscle mass, muscle size and absolute muscle strength in mouse muscle along with a significant decrease in muscle degeneration and concentrations of serum creatine kinase.

Melanocortin receptor-4 (MCR-4) blockers increase food intake, decrease energy expenditure, and cause weight gain. It has been demonstrated, in experimental studies, that MC4-R blockade protects animals against cancer-induced anorexia (Foster et al., 2005). Moreover, Markison et al. (2005) have shown that a selective MC4-R antagonist, administered peripherally was able to reduce tumor induced anorexia and increase lean body mass in comparison with placebo.

Conclusion

Despite the major improvements in cancer treatment in the last decades, CC continues to represent as a common problem occurring in a large proportion of patients. Cancer related anorexia and cachexia adversely affects patient outcome and is associated with poor response to treatment against cancer, susceptibility to treatment related toxicity and complications, poor quality of life and mortality. Current treatment for CC principally depends on its prevention rather than reversing the disease state. In the last few years, a large amount of drugs have been tested in experimental animal models and in preliminary human trials, with promising results. Yet, a significant percent of patients die due to CC resistant to traditional strategies. But fortunately our knowledge of cellular and molecular mechanisms causing CC is progressively accumulating. The future therapies will be aimed to inhibit the steps of pathways leading to muscle atrophy. But, currently it appears to be logical to accept CC as an early disease step which is triggered at the beginning of disease when even no weight loss is detected, and fight against it before its advance to an irreversible condition. For this purpose, till the invention of effective medications, early onset

nutritional support and medications including megesterol acetate, and anti-inflammatory agents, such as EPA should be an effective strategy in prevention and somehow treatment of cancer related anorexia and cachexia.

In summary, although there is too much to be done for both prevention and treatment of CC, currently it appears to be logical to evaluate patients for existence of cancer-related anorexia and cachexia during diagnosis of cancer even in the absence of apparent weight loss and use the preventive measures including nutritional support and medications appropriate for the patients medical conditions till the invention of effective treatment modalities. Finally, prevention of the treatment related morbidities including nausea, vomiting, dysphagia, mucositis, diarrhea, pain, and depression may positively impact the patients QoL and treatment results against both cancer itself and related cachexia.

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